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TRANSMITTAL OF CERTIFIED PRIORITY DOCUMENT UNDER 35 USC §119

In accordance with the provisions of 35 U.S.C. §119, applicants hereby claim priority of Swedish Patent application No. 0003435-5, filed September 26, 2000. A certified copy of the application is submitted herewith. As the priority application is in the English language, all of the requirements of §119 have been met.

Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 13425-042001.

Respectfully submitted,

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PROMOTER SEQUENCES

TECHNICAL FIELD

The present invention relates an isolated promoter region of the mammalian transcription factor *FOXC2*. The invention also relates to screening methods for agents modulating the expression of *FOXC2* and thereby being potentially useful for the treatment of medical conditions related to obesity. The invention further relates to a previously unknown variant of the human *FOXC2* gene, derived via the use of an alternative promoter, which produces an additional exon that generates a distinct open reading frame via splicing. The alternative gene encodes a variant of the FOXC2 transcription factor, which is lacking a part of the DNA-binding domain and consequently has a potential regulatory function.

BACKGROUND ART

More than half of the men and women in the United States, 30 years of age and older, are now considered overweight, and nearly one-quarter are clinically obese. This high prevalence has led to increases in the medical conditions that often accompany obesity, especially non-insulin dependent diabetes mellitus (NIDDM), hypertension, cardiovascular disorders, and certain cancers. Obesity results from a chronic imbalance between energy intake (feeding) and energy expenditure. To better understand the mechanisms that lead to obesity and to develop strategies in certain patient populations to control obesity, there is a need to develop a better underlying knowledge of the molecular events that regulate the differentiation of preadipocytes and stem cells to adipocytes, the major component of adipose tissue.

The helix-loop-helix (HLH) family of transcriptional regulatory proteins are key players in a wide array of developmental processes (for a review, see Massari & Murre (2000) Mol. Cell. Biol. 20: 429-440). Over 240 HLH proteins have been identified to date in organisms ranging from the yeast *Saccharomyces cerevisiae* to humans. Studies in *Xenopus laevis*, *Drosophila melanogaster*, and mice have convincingly demonstrated that HLH proteins are intimately involved in developmental events such as cellular differentiation, lineage

commitment, and sex determination. In multicellular organisms, HLH factors are required for a multitude of important developmental processes, including neurogenesis, myogenesis, hematopoiesis, and pancreatic development.

The winged helix / forkhead class of transcription factors is characterized by a 100-amino acid, monomeric DNA-binding domain. X-ray crystallography of the forkhead domain from HNF-3γ has revealed a three-dimensional structure, the "winged helix", in which two loops (wings) are connected on the C-terminal side of the helix-loop-helix (for reviews, see Brennan, R.G. (1993) Cell 74: 773-776; and Lai, E. et al. (1993) Proc. Natl. Acad. Sci. U.S.A. 90: 10421-10423).

The isolation of the mouse mesenchyme forkhead-1 (MFH-1) and the corresponding human (*FKHL14*) chromosomal genes is disclosed by Miura, N. et al. (1993) FEBS letters 326: 171-176; and (1997) Genomics 41: 489-492. The nucleotide sequences of the mouse MFH-1 gene and the human *FKHL14* gene have been deposited with the EMBL/GenBank Data Libraries under accession Nos. Y08222 (SEQ ID NO: 5) and Y08223 (SEQ ID NO: 8), respectively. A corresponding gene has been identified in *Gallus gallus* (GenBank accession numbers U37273 and U95823).

The International Patent Application WO 98/54216 discloses a gene encoding a Forkhead-Related Activator (FREAC)-11 (also known as S12), which is identical with the polypeptide encoded by the human *FKHL14* gene disclosed by Miura, *supra*. This transcription factor is expressed in adipose tissue and involved in lipid metabolism and adipocyte differentiation (cf. Swedish patent application No. 0000531-4, filed February 18, 2000).

The nomenclature for the winged helix / forkhead transcription factors has been standardized and Fox (Forkhead Box) has been adopted as the unified symbol (Kaestner et al. (2000) Genes & Development 14: 142-146; see also *htpp://www.biology.pomona.edu/fox*). It has been agreed that the genes previously designated MFH-1 and *FKHL14* (as well as FREAC-11 and S12) should be designated *FOXC2*.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the general structure of the human *FOXC2* gene.

Figure 2 illustrates the results from phylogenetic footprinting experiments. Shown is the fraction conserved (1.0 = 100%) between mouse FoxC2 and human *FOXC2* sequences in the alignment generated with Clustal. Solid (bold) line indicates the fraction of the human sequence which is identical to the mouse within a 200 bp "window" over the human sequence in the alignment. The weak (dotted) line is set to -0.05 when the sliding window contains human exon sequence and to –0.1 when the window is entirely composed of exon sequence. Regions containing local maxima or exceeding a conservation fraction of 0.7 are likely to be functional and are classified as "predicted regulatory regions".

Figure 3 illustrates the predicted "enhancer" region in the human *FOXC2* gene. Underlined sequences indicate likely transcription factor binding sites. Boxed sequence indicates exon sequence.

Splice = sequence predicted as splice site in the alternatively spliced gene;

E-box-like = sequence resembling the "E-box" motif CANNTG known as a target for DNA binding proteins containing a helix-loop-helix domain (often associated with the activation of cell-type specific gene transcription during tissue differentiation; see Massari & Murre (2000) Mol. Cell. Biol. 20: 429-440)

Forkhead-like = sequence resembling binding site for the winged helix / forkhead class of transcription factors;

Ets-like = sequence resembling consensus binding site for ETS-domain transcription factor family (see Sharrocks et al. (1997) Int. J. Biochem. Cell Biol. 29, 1371-1387).

Figure 4 illustrates the predicted "promoter" region in the human *FOXC2* gene. Underlined sequence indicates exon sequences. Boxed sequences indicate conserved block (potential transcription factor binding sites).

DESCRIPTION OF THE INVENTION

According to the present invention, the partially known sequence (SEQ ID NO: 8) of human FOXC2 gene has been extended. In the previously unknown region of the gene, differentially conserved regions, consistent with regulatory function, have been identified. Further, an alternative transcript has been identified, which includes the use of at least two exons. The putative regulatory enhancer is immediately adjacent to the newly discovered alternative exon, suggesting that it may play a role in the alternative selection of transcript classes.

Modulation of the *FOXC2* regulation is expected to have therapeutic value in type II diabetes; obesity, hypercholesterolemia, and other cardiovascular diseases or dyslipidemias.

Consequently, in a first aspect this invention provides a human *FOXC2* promoter region comprising a sequence selected from:
(a) the nucleotide sequence set forth as positions 1250 to 2235, such as positions 1250 to 1749 or positions 1692 to 1703, in SEQ ID NO: 1, or a fragment thereof exhibiting *FOXC2* promoter activity;
(b) the complementary strand of (a); and
(c) nucleotide sequences capable of hybridizing, under stringent hybridization conditions, to a nucleotide sequence as defined in (a) or (b).

Another aspect of the invention is a recombinant construct comprising the human *FOXC2* promoter region as defined above. In the said recombinant construct, the human *FOXC2* promoter region can be operably linked to a gene encoding a detectable product, such as the human *FOXC2* gene, or a reporter gene. The term "operably linked" as used herein means functionally fusing a promoter with a structural gene in the proper frame to express the structural gene under control of the promoter. As used herein, the term "reporter gene" means a gene encoding a gene product that can be identified using simple, inexpensive methods or reagents and that can be operably linked to the human *FOXC2* promoter region or an active fragment thereof. Reporter genes such as, for example, a luciferase, β-galactosidase, alkaline phosphatase, or green fluorescent protein reporter gene, can be used

to determine transcriptional activity in screening assays according to the invention (see, for example, Goeddel (ed.), Methods Enzymol., Vol. 185, San Diego: Academic Press, Inc. (1990); see also Sambrook, *supra*).

The invention also provides a vector comprising the recombinant construct as defined above, as well as a host cell stably transformed with such a vector, or generally with the recombinant construct according to the invention. The term "vector" refers to any carrier of exogenous DNA that is useful for transferring the DNA to a host cell for replication and/or appropriate expression of the exogenous DNA by the host cell.

In another aspect, the invention provides a method for identification of an agent regulating *FOXC2* promoter activity, said method comprising the steps: (i) contacting a candidate agent with a human *FOXC2* promoter region as defined above; and (ii) determining whether said candidate agent modulates expression of the *FOXC2* gene, such modulation being indicative for an agent capable of regulating *FOXC2* promoter activity. As used herein, the term "agent" means a biological or chemical compound such as a simple or complex organic molecule, a peptide, a protein or an oligonucleotide.

A transfection assay can be a particularly useful screening assay for identifying an effective agent. In a transfection assay, a nucleic acid containing a gene such as a reporter gene that is operably linked to a human *FOXC2* promoter, or an active fragment thereof, is transfected into the desired cell type. A test level of reporter gene expression is assayed in the presence of a candidate agent and compared to a control level of expression. An effective agent is identified as an agent that results in a test level of expression that is different than a control level of reporter gene expression, which is the level of expression determined in the absence of the agent. Methods for transfecting cells and a variety of convenient reporter genes are well known in the art (see, for example, Goeddel (ed.), Methods Enzymol., Vol. 185, San Diego: Academic Press, Inc. (1990); see also Sambrook, *supra*). Consequently, the said method could e.g. comprising assaying reporter gene expression in a host cell, stably transformed with a recombinant construct comprising the human FOXC2 promoter, in the presence and absence of a candidate agent, wherein an effect on the test level of expression as compared to control level of expression is indicative of an agent capable of regulating *FOXC2* promoter activity.

In a further aspect, the invention provides a human *FOXC2* enhancer region comprising a sequence selected from:
(a) the nucleotide sequence set forth as positions 216 to 475, such as positions 223 to 231, positions 359 to 375, positions 378 to 402, or positions 403 to 423, in SEQ ID NO: 1, or a fragment thereof exhibiting *FOXC2* enhancer activity;
(b) the complementary strand of (a); and
(c) nucleotide sequences capable of hybridizing, under stringent hybridization conditions, to a nucleotide sequence as defined in (a) or (b).

As described above for the human *FOXC2* promoter region, the invention further provides a recombinant construct comprising a human *FOXC2* enhancer region, a vector comprising the said recombinant construct, as well as a host cell stably transformed with said vector or with said recombinant construct.

Further, the invention provides a method for identification of an agent regulating *FOXC2* enhancer activity, said method comprising the steps: (i) contacting a candidate agent with the human *FOXC2* enhancer region as defined above; and (ii) determining whether said candidate agent modulates expression of the *FOXC2* gene, such modulation being indicative for an agent capable of regulating *FOXC2* enhancer activity. It will be understood by the skilled person that known steps are available for performing such a method. For instance, a "panel" of constructs which include a variety of mutations and deletions can be used in order to associate a response with a specific alteration of a single base or subsegment of the regulatory apparatus. A simple panel might include: enhancer plus promoter, promoter only, enhancer plus a "minimal" promoter from a distinct gene. As mentioned above, a transfection assay, using a host cell stably transformed with a suitable recombinant construct, can be a particularly useful screening assay for identifying an effective agent.

In yet a further aspect, the invention provides a method for identification of an agent capable of regulating a mammalian *FOXC2* promoter activity, said method comprising the steps (i) contacting a candidate agent with a murine *FoxC2* promoter nucleotide sequence shown as positions 216 to 2235, such as positions 216 to 475 or positions 1250 to 2235, in

SEQ ID NO: 5; and (ii) determining whether said candidate agent modulates expression of a mammalian *FOXC2* gene, such modulation being indicative for an agent capable of regulating mammalian *FOXC2* promoter activity.

In another important aspect, the invention provides an isolated nucleic acid molecule selected from:

(a) nucleic acid molecules comprising a nucleotide sequence as shown in SEQ ID NO: 3;

(b) nucleic acid molecules comprising a nucleotide sequence capable of hybridizing, under stringent hybridization conditions, to a nucleotide sequence complementary the polypeptide coding region of a nucleic acid molecule as defined in (a) and which codes for a variant form of the FOXC2 transcription factor; and

(c) nucleic acid molecules comprising a nucleic acid sequence which is degenerate as a result of the genetic code to a nucleotide sequence as defined in (a) or (b) and which codes for a variant form of the FOXC2 transcription factor.

In a preferred form of the invention, the said nucleic acid molecule has a nucleotide sequence identical with SEQ ID NO: 3 of the Sequence Listing. However, the nucleic acid molecule according to the invention is not to be limited strictly to the sequence shown as SEQ ID NO: 3. Rather the invention encompasses nucleic acid molecules carrying modifications like substitutions, small deletions, insertions or inversions, which nevertheless encode proteins having substantially the biochemical activity of the FOXC2 polypeptide according to the invention. Included in the invention are consequently nucleic acid molecules, the nucleotide sequence of which is at least 90% homologous, preferably at least 95% homologous, with the nucleotide sequence shown as SEQ ID NO: 3 in the Sequence Listing.

Included in the invention is also a nucleic acid molecule which nucleotide sequence is degenerate, because of the genetic code, to the nucleotide sequence shown as SEQ ID NO: 3. A sequential grouping of three nucleotides, a "codon", codes for one amino acid. Since there are 64 possible codons, but only 20 natural amino acids, most amino acids are coded for by more than one codon. This natural "degeneracy", or "redundancy", of the genetic code is well known in the art. It will thus be appreciated that the nucleotide sequence

shown in the Sequence Listing is only an example within a large but definite group of sequences which will encode the variant FOXC2 polypeptide.

The invention includes an isolated polypeptide encoded by the nucleic acid as defined above. In a preferred form, the said polypeptide has an amino acid sequence according to SEQ ID NO: 4 of the Sequence Listing. However, the polypeptide according to the invention is not to be limited strictly to a polypeptide with an amino acid sequence identical with SEQ ID NO: 4 in the Sequence Listing. Rather the invention encompasses polypeptides carrying modifications like substitutions, small deletions, insertions or inversions, which polypeptides nevertheless have substantially the biological activities of the variant FOXC2 polypeptide.

A further aspect of the invention is a vector harboring the nucleic acid molecule according to the invention. The said vector can e.g. be a replicable expression vector, which carries and is capable of mediating the expression of a DNA molecule according to the invention. In the present context the term "replicable" means that the vector is able to replicate in a given type of host cell into which is has been introduced. Examples of vectors are viruses such as bacteriophages, cosmids, plasmids and other recombination vectors. Nucleic acid molecules are inserted into vector genomes by methods well known in the art.

Included in the invention is also a cultured host cell harboring a vector according to the invention. Such a host cell can be a prokaryotic cell, a unicellular eukaryotic cell or a cell derived from a multicellular organism. The host cell can thus e.g. be a bacterial cell such as an *E. coli* cell; a cell from yeast such as *Saccharomyces cervisiae* or *Pichia pastoris*, or a mammalian cell. The methods employed to effect introduction of the vector into the host cell are standard methods well known to a person familiar with recombinant DNA methods.

In yet another aspect, the invention includes a method for identifying an agent capable of regulating expression of the nucleic acid molecule as defined above, said method comprising the steps (i) contacting a candidate agent with the said nucleic acid molecule; and (ii) determining whether said candidate agent modulates expression of the said nucleic acid molecule.

In another aspect the invention provides an antisense oligonucleotide having a sequence capable of specifically hybridizing to RNA transcribed by the alternatively spliced nucleic acid molecule shown as SEQ ID NO: 3, so as to prevent translation of the said RNA. Antisense nucleic acids (preferably 10 to 20 base-pair oligonucleotides) capable of specifically binding to control sequences for the alternatively spliced *FOXC2* gene are introduced into cells, e.g. by a viral vector or colloidal dispersion system such as a liposome. The antisense nucleic acid binds to the target nucleotide sequence in the cell and prevents transcription and/or translation of the target sequence. Phosphorothioate and methylphosphonate antisense oligonucleotides are specifically contemplated for therapeutic use by the invention. Suppression of expression of the alternatively spliced FOXC2 gene, at either the transcriptional or translational level, is useful to generate cellular or animal models for diseases/conditions related to lipid metabolism.

Throughout this description the terms "standard protocols" and "standard procedures", when used in the context of molecular biology techniques, are to be understood as protocols and procedures found in an ordinary laboratory manual such as: Current Protocols in Molecular Biology, editors F. Ausubel et al., John Wiley and Sons, Inc. 1994, or Sambrook, J., Fritsch, E.F. and Maniatis, T., Molecular Cloning: A laboratory manual, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY 1989.

EXAMPLES

Additional features of the invention will be apparent from the following Examples. Examples 1 to 4 are actual, while the remaining Examples are prophetic.

EXAMPLE 1: Computational identification of *FOXC2* genomic sequences

The sequences present in the GenBank database *(http://www.ncbi.nlm.nih.gov)* were screened for sequence similarity to the human *FOXC2* cDNA sequence (GenBank accession number NM_00521 (SEQ ID NO: 9)). The BLAST algorithm (Altschul et al. (1997) Nucleic Acids Res. 25:3389-3402) was used for determining sequence identity.

Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information *(http://www.ncbi.nlm.nih.gov)*. A working draft genomic sequence in 25 unordered pieces, from the *Homo sapiens* chromosome 16 clone RP11-463O9 (GenBank accession number AC009108; Version 6; GI:7689930; released 4 May 2000), was selected for further studies.

Regions in sequence AC009108 matching portions of the *FOXC2* cDNA sequence NM_005251were combined using the PHRAP software, developed at the University of Washington *(http://www.genome.washington.edu/UWGC/analysistools/phrap.htm)*. Two contigs of 9780 bp (positions 116445 to 126224 in GenBank AC009108.6) and 3784 bp (positions 42927 to 46710 in GenBank AC0091108.6), respectively, were assembled to generate a human *FOXC2* genomic fragment of 13451 bp.

The ClustalW multiple sequence alignment program, version 1.8 (Thompson et al. (1994) Nucleic Acids Research 22: 4673-4680), was then used to identify the human *FOXC2* extended genomic DNA sequence of 6458 bp (SEQ ID NO: 1) by comparison with the mouse cDNA sequence X74040 (SEQ ID NO: 6). First, a 6459 bp sequence, corresponding to positions 1500–7958 in the 13451 bp sequence, was selected. Positions 1–2285 in this 6459 bp sequence corresponded to 44426–46710 in AC009108.6, while positions 2151–6459 corresponded to positions 126224–121916 (reverse complement taken) in AC009108.6. The overlap of positions 2151-2285 allowed for the contigs to be joined by the assembly program. The G residue in position 2655 was considered to be a sequencing error and was removed, which resulted in the 6458 bp sequence set forth as SEQ ID NO: 1. The open reading frame in SEQ ID NO: 1 encodes a polypeptide (SEQ ID NO: 2) identical with the known human FOXC2 polypeptide shown as SEQ ID NO:10.

EXAMPLE 2: Identification of potential regulatory sequences in the human and mouse *FOXC2* genomic sequences

In phylogenetic footprinting (for a review, see Duret & Bucher (1997) Current Opinion in Structural Biology 7(3): 399-406) sequences are aligned and a regional sequence identity is determined for each window of a fixed, arbitrary length. This allows the identification of

potential regulatory regions in genomic sequences. Non-exon sequences that are conserved over the course of evolution are likely to perform regulatory roles. Phylogenetic footprinting was performed as described in Wasserman & Fickett (1998) J. Mol. Biol. 278, 167-181, based on an alignment generated with the ClustalW multiple sequence alignment program, version 1.8 (Thompson et al. (1994) Nucleic Acids Research 22: 4673-4680), with default parameters adjusted to a gap opening penalty of 20 and a gap extension penalty of 0.2. The human (SEQ ID NO: 1) and mouse (SEQ ID NO: 5) genomic sequences were aligned. Percentage identity was plotted for each contiguous 200 bp segment of the human gene to identify segments differentially conserved (in comparison to adjoining sequences) (Fig. 2).

In addition to segments of the published exon sequence, two differentially conserved regions or "footprints" were identified in the human gene. Both of these regions are local maxima and contain segments which exceed 70% nucleotide identity between the human and mouse genomic sequences. One region, shown as positions 1250 to 2235, in particular positions 1250 to 1749, in SEQ ID NO: 1, immediately adjacent to the published exon region, is likely to contain the transcription start site and proximal promoter regulatory sequences (Fig. 4). Another region, shown as positions 216 to 475 in SEQ ID NO: 1, approximately 1700 bp distal from the transcription start site, is likely to function as some form of regulatory region (either enhancer or repressor) (Fig. 3). (A schematic overview of the extended *FOXC2* gene is shown in Fig. 1.)

Further analysis of these regulatory regions identified short segments of higher conservation between the mouse and human genes, suggesting that these specific segments function as transcription factor binding sites. Screening of the TRANSFAC transcription factor database *(http://transfac.gbf.de)* (see Wingender et al. (2000) Nucleic Acids Research 28(1): 316-319) for matches to known transcription factors suggested the presence of multiple forkhead-like binding sites in the distal regulatory enhancer, which suggests potential auto-regulation of FOXC2 by its protein product.

A third region containing a local maxima for conservation and a segment exceeding 70% identity is present at the 3' end of the published exon sequence within the 3' UTR. This conserved region may have a role in mRNA processing.

The same analysis was performed with reference to 200 bp contiguous segments of the mouse *FoxC2* genomic sequence (SEQ ID NO: 5). The following conserved regions were identified: 190 to 420; 1070 to 1645; and 5580 to 5875. They correlate to the regions indicated above for the human sequence and should be considered orthologous regions.

EXAMPLE 3: Identification of an alternative human *FOXC2* cDNA sequence

BLASTN screening of the dbEST database from GenBank, using the human FOXC2 cDNA (SEQ ID NO: 9) as a query sequence, revealed several ESTs overlapping containing portions of the available cDNA. A specialized tool, est_genome *(http://www.sanger.ac.uk)*, for the prediction of exon boundaries using ESTs was applied to compare the EST sequences to the genomic sequences (See Mott, R. (1997) Computer Applications in the Biosciences 13(4): 477-478). Two classes of ESTs were observed: sequences extending into the 3'-untranslated region and sequences revealing an alternative first exon spliced to a junction internal to the previously described first exon.

Specifically, it was found that the nucleotides in positions 33 to 182 in the EST with accession no. AW271272 (SEQ ID NO: 11) were identical to positions 66 to 215 in the extended *FOXC2* genomic sequence (SEQ ID NO: 1), and that positions 183 to 327 in SEQ ID NO: 11 were identical to positions 2516 to 2660 in SEQ ID NO: 1. Similarly, positions 5 to 55 in the EST with accession no. AW793237 (SEQ ID NO: 12) were identical to positions 165 to 215 in the extended *FOXC2* genomic sequence (SEQ ID NO: 1), and positions 56 to 157 in SEQ ID NO: 12 were identical to positions 2516 to 2607 in SEQ ID NO: 1. These results revealed an alternative splicing pattern in the human *FOXC2* gene. According to this splicing pattern, an alternative gene sequence (SEQ ID NO: 3) is derived by joining the regions shown as positions 1–215 and 2516–6458 in SEQ ID NO: 1. Alternative splicing patterns are known to regulate the synthesis of a variety of peptides and proteins. It may result in proteins with an entirely different function or in dysfunctional or inhibitory splice products (for a review, see McKeown (1992) Annu. Rev. Cell. Biol. 8: 133-155).

The amino acids corresponding to positions 1 to 94 in the published FOXC2 transcription factor (SEQ ID NO: 10) are missing in protein encoded by the spliced variant generated from the alternative promoter (SEQ ID NO: 4). Consequently, the entire region N-terminal of the DNA binding domain and a portion of the DNA-binding domain (corresponding to positions 72-94 in SEQ ID NO: 2) are not present in the splice variant. It is postulated that this truncation leads to a protein which has a deficient "forkhead" DNA-binding region, and thus has a potential inhibitory function on the biological activities of the FOXC2 protein. This truncated FOXC2 protein may have a role in regulation of FOXC2, and an involvment in adipocyte differentiation and adipogenesis.

EXAMPLE 4: Cloning and sequencing of the FOXC2 promoter

The DNA region corresponding to nucleotide 176 to nucleotide 2233 (SEQ ID NO. 1 version 2) has been cloned using nested PCR on human genomic DNA. The PCR was performed according the Herculase™ protocol (Stratagene catalog #600260; *http://www.stratagene.com/pcr/herculase.htm*) and with the inclusion of 8-10% DMSO.

In the initial reaction, the 5'-primer KRKX131 (CCATTGCCTTCTAGTCGCCTCC) was used together with the 3'-primer KRKX133 (CGTTGGGGTCGGACACGGAGTA) using 250 ng Clontech Genomic DNA # 6550-1 as template. The nested reaction was performed on 1/100 of the initial PCR reaction using the 5'-primer KRKX132 (GGTACCTACGCAGCCGATGAACAGCCA) and the 3'-primer KRKX134 (GCTAGCGCTGCTTCCGAGACGGCTCG). After the second PCR, the product was analyzed by electrophoresis in a 1.2% agarose gel, and a PCR product of the expected size was obtained and extracted for ligation into a TOPO PCR2.1 vector (Invitrogen, Carlsbad, CA) by standard cloning procedures and thereafter sequenced. The PCR reaction and cloning procedure was repeated in two parallel separate experiments, and sequence data from the two separate reactions were compared with the bioinformatically assembled sequence.

A DNA region containing the promoter (Fig. 4) corresponding to nt1179 to 2233 (SEQ ID NO: 1, version 2) was has been cloned using nested PCR in the same manner as described

above. In the initial reaction, the 5'-primer KRKX136 (GGTACCCCCCGAGCCTGGAAACTCCCT) was used together with the 3'-primer KRKX134 (GCTAGCGCTGCTTCCGAGACGGCTCG) using 250 ng genomic DNA as a template. The PCR reaction and cloning procedure was repeated in four parallel separate experiments, and sequence data from the four separate reactions were compared with the bioinformatically assembled sequence.

EXAMPLE 5: Tissue expression profiling of the alternative transcript

Tissue expression profiling of the alternative transcript (SEQ ID NO: 3) is performed using standard Northern blotting procedures. RNA samples from an array of human tissues, including adipose tissue, are analyzed using an RNA or DNA probe specific for the alternative transcript. The expression profile in adipose tissue could be indicative a putative regulatory function for the alternative gene product (SEQ ID NO: 4) on adipogenesis and adipocyte differentiation.

In addition, reverse transcriptase PCR (RT-PCR) according to standard procedures is used to detect very low level expression of the alternative transcript in adipose tissue. RNA is prepared from human adipose tissue, and RT-PCR is performed using PCR primers specific for the alternative transcript.

EXAMPLE 6: Mapping of the 5'-edge of the alternative exon by RACE-PCR

RNA is prepared from human adipose tissue using standard protocols. RACE (Rapid Amplification of cDNA Ends) PCR is performed using the SMART™ RACE cDNA Amplification Kit (Clontech catalogue No. K1811-1; *http://www.clontech.com/product/catalog/PCR/smartrace.html*). With this procedure, the first strand synthesis produces cDNA with an extension containing a known sequence. Due to the mechanism of the extension procedure, the extension is typically added only to complete first strand cDNAs. The 5'-RACE PCR is then performed using the 5'-primer provided with the kit, together with a 3'-primer corresponding to positions 210-237 in SEQ ID NO: 3

(GAACTGGTAGATGCCGTTCAAGGTTTCC) specific for the alternative transcript. The PCR product is cloned into a cloning vector and sequenced using standard protocols.

EXAMPLE 7: Functional analysis

The identified regulatory regions are analyzed to determine their impact on the transcription of the *FOXC2* gene or a reporter gene substituted for *FOXC2*. A PCR reaction is performed to isolate the promoter region adjacent to the published exon sequence, possibly including the sequences extending to the beginning of the ATG encoding the first methionine. This PCR product is cloned into a reporter plasmid adjacent to a reporter gene (e.g. luciferase). The upstream regulatory region, i.e. regions containing both upstream and promoter proximal sequences, or these sequences bearing artificially induced differences, are cloned in a similar manner. These constructs are transfected into a cell culture model system and the level/activity of the protein encoded by the reporter gene is determined. This would provide information on the function of the identified regions, and used to assess the impact of the different regions on transcriptional regulation. Similarly, the upstream regulatory region, a region containing both upstream and promoter proximal sequences, or these sequences bearing artificially induced differences can be cloned and used to assess the impact of these regions on the transcription of the reporter gene.

EXAMPLE 8: Reporter gene assay to identify modulating compounds

Reporter gene assays are well known as tools to signal transcriptional activity in cells. (For a review of chemiluminescent and bioluminescent reporter gene assays, see Bronstein et al. (1994) Analytical Biochemistry 219, 169-181.) For instance, the photoprotein luciferase provides a useful tool for assaying for modulators of promoter activity. Cells are transiently transfected with a reporter construct which includes a gene for the luciferase protein downstream from the FOXC2 promoter and enhancer region, or fragments thereof regulating the FOXC2 activity. Luciferase activity may be quantitatively measured using e.g. luciferase assay reagents that are commercially available from Promega (Madison,

WI). Differences in luminescence in the presence versus the absence of a candidate modulator compound are indicative of modulatory activity.

TABLE I

Summary of *FOXC2* sequences

SEQ ID NO:	GenBank accession no.	Description
1		Human *FOXC2* extended genomic DNA sequence
2		Human *FOXC2* polypeptide sequence (Identical with SEQ ID NO: 10)
3		Human *FOXC2* DNA sequence Alternative splicing
4		Human polypeptide sequence Alternative open reading frame
5	Y08222	Mouse MHF-1 (*FoxC2*) genomic DNA sequence (CDS 2070 – 3554)
6	X74040	Mouse MHF-1 (*FoxC2*) cDNA sequence
7		Mouse MHF-1 (*FoxC2*) polypeptide sequence
8	Y08223	Human *FKHL14 (FOXC2)* genomic DNA sequence (CDS 1197 – 2702)
9	NM_005251	Human *FKHL14 (FOXC2)* cDNA sequence
10		Human *FKHL14 (FOXC2)* polypeptide sequence
11	AW 271272	Human EST
12	AW 793237	Human EST

TABLE II

Summary of features in human *FOXC2* sequences shown as SEQ ID NOs: 1 and 3

Feature	Positions
SEQ ID NO: 1	
First exon according to the alternative transcript	1 – 215
– Untranslated region	1 – 186
– Region coding for 5'-part of alternative protein	187 – 215
Alternative first exon splice site	215 – 216
Predicted enhancer region	216 – 475
– E-box-like region	223 – 231
– Forkhead-like region	359 – 375
– Forkhead-like region	378 – 402
– Ets-like region	403 – 423
Predicted promoter region	1250 – 1749
– Forkhead-like region	1692 – 1703
First exon according to the published form of the transcript	1746 – 4629
– Untranslated region	1746 – 2234
– Polypeptide coding region	2235 – 3740
– Region coding for DNA-binding domain	2448 – 2735
Second exon according to the alternative transcript	2516 – 4629
– Portion of polypeptide used in alternative transcript	2516 – 3740
– Untranslated region	3741 – 4629
SEQ ID NO: 3	
Polypeptide coding region (5' of splice site)	187 – 215
Polypeptide coding region (3' of splice site)	216 – 1437
– Region coding for truncated portion of protein	216 – 435

CLAIMS

1. A human *FOXC2* promoter region comprising a sequence selected from:
(a) the nucleotide sequence set forth as positions 1692 to 1703 in SEQ ID NO: 1, or a fragment thereof exhibiting *FOXC2* promoter activity;
(b) the complementary strand of (a); and
(c) nucleotide sequences capable of hybridizing, under stringent hybridization conditions, to a nucleotide sequence as defined in (a) or (b).

2. The human *FOXC2* promoter region according to claim 1, comprising a sequence selected from:
(a) the nucleotide sequence set forth as positions 1250 to 1749 in SEQ ID NO: 1, or a fragment thereof exhibiting *FOXC2* promoter activity;
(b) the complementary strand of (a); and
(c) nucleotide sequences capable of hybridizing, under stringent hybridization conditions, to a nucleotide sequence as defined in (a) or (b).

3. The human *FOXC2* promoter region according to claim 2, comprising a sequence selected from:
(a) the nucleotide sequence set forth as positions 1250 to 2235 in SEQ ID NO: 1, or a fragment thereof exhibiting *FOXC2* promoter activity;
(b) the complementary strand of (a); and
(c) nucleotide sequences capable of hybridizing, under stringent hybridization conditions, to a nucleotide sequence as defined in (a) or (b).

4. A recombinant construct comprising the human *FOXC2* promoter region according to any one of claims 1 to 3.

5. The recombinant construct according to claim 4 wherein the human *FOXC2* promoter region is operably linked to a gene encoding a detectable product.

6. The recombinant construct according to claim 5 wherein said gene encoding a detectable product is a human *FOXC2* gene.

7. The recombinant construct according to claim 4 further comprising a reporter gene.

8. A vector comprising the recombinant construct according to any one of claims 4 to 7.

9. A host cell stably transformed with the recombinant construct according to any one of claims 4 to 7.

10. A method for identification of an agent regulating *FOXC2* promoter activity, said method comprising the steps
(i) contacting a candidate agent with a human *FOXC2* promoter region as defined in any one of claims 1 to 3; and
(ii) determining whether said candidate agent modulates expression of the *FOXC2* gene, such modulation being indicative for an agent capable of regulating *FOXC2* promoter activity.

11. A method for identification of an agent regulating *FOXC2* promoter activity, said method comprising assaying reporter gene expression in a cell according to claim 9 in the presence and absence of a candidate agent, wherein an effect on the test level of expression as compared to control level of expression is indicative of an agent capable of regulating *FOXC2* promoter activity.

12. A human *FOXC2* enhancer region comprising a sequence selected from:
(a) the nucleotide sequence set forth as positions 223 to 231 in SEQ ID NO: 1, or a fragment thereof exhibiting *FOXC2* enhancer activity;
(b) the complementary strand of (a); and
(c) nucleotide sequences capable of hybridizing, under stringent hybridization conditions, to a nucleotide sequence as defined in (a) or (b).

13. A human *FOXC2* enhancer region comprising a sequence selected from:
(a) the nucleotide sequence set forth as positions 359 to 375 in SEQ ID NO: 1, or a fragment thereof exhibiting *FOXC2* enhancer activity;
(b) the complementary strand of (a); and

(c) nucleotide sequences capable of hybridizing, under stringent hybridization conditions, to a nucleotide sequence as defined in (a) or (b).

14. A human *FOXC2* enhancer region comprising a sequence selected from:
(a) the nucleotide sequence set forth as positions 378 to 402 in SEQ ID NO: 1, or a fragment thereof exhibiting *FOXC2* enhancer activity;
(b) the complementary strand of (a); and
(c) nucleotide sequences capable of hybridizing, under stringent hybridization conditions, to a nucleotide sequence as defined in (a) or (b).

15. A human *FOXC2* enhancer region comprising a sequence selected from:
(a) the nucleotide sequence set forth as positions 403 to 423 in SEQ ID NO: 1, or a fragment thereof exhibiting *FOXC2* enhancer activity;
(b) the complementary strand of (a); and
(c) nucleotide sequences capable of hybridizing, under stringent hybridization conditions, to a nucleotide sequence as defined in (a) or (b).

16. The human *FOXC2* enhancer region according to any one of claims 12 to 15 comprising a sequence selected from:
(a) the nucleotide sequence set forth as positions 216 to 475 in SEQ ID NO: 1, or a fragment thereof exhibiting *FOXC2* enhancer activity;
(b) the complementary strand of (a); and
(c) nucleotide sequences capable of hybridizing, under stringent hybridization conditions, to a nucleotide sequence as defined in (a) or (b).

17. A recombinant construct comprising a human *FOXC2* enhancer region according to any one of claims 12 to 15.

18. A vector comprising the recombinant construct according to claim 17.

19. A host cell stably transformed with the recombinant construct according to claim 18.

20. A method for identification of an agent regulating *FOXC2* enhancer activity, said method comprising the steps
(i) contacting a candidate agent with the human *FOXC2* enhancer region as defined in any one of claims 12 to 16; and
(ii) determining whether said candidate agent modulates expression of the *FOXC2* gene, such modulation being indicative for an agent capable of regulating *FOXC2* enhancer activity.

21. A method for identification of an agent capable of regulating *FOXC2* enhancer activity, said method comprising assaying reporter gene expression in a cell as defined in claim 19 in the presence and absence of a candidate agent, wherein an effect on the test level of expression as compared to control level of expression is indicative of an agent capable of regulating *FOXC2* enhancer activity.

22. A method for identification of an agent capable of regulating a mammalian *FOXC2* promoter activity, said method comprising the steps
(i) contacting a candidate agent with a murine *FoxC2* promoter nucleotide sequence shown as positions 1250 to 2235 in SEQ ID NO: 5; and
(ii) determining whether said candidate agent modulates expression of a mammalian *FOXC2* gene, such modulation being indicative for an agent capable of regulating mammalian *FOXC2* promoter activity.

23. A method for identification of an agent capable of regulating a mammalian *FOXC2* enhancer activity, said method comprising the steps
(i) contacting a candidate agent with a murine *FoxC2* enhancer nucleotide sequence shown as positions 216 to 475 in SEQ ID NO: 5; and
(ii) determining whether said candidate agent modulates expression of a mammalian *FOXC2* gene, such modulation being indicative for an agent capable of regulating mammalian *FOXC2* enhancer activity.

24. A method for identification of an agent capable of regulating a mammalian *FOXC2* enhancer activity, said method comprising the steps

(i) contacting a candidate agent with a murine *FoxC2* enhancer nucleotide sequence shown as positions 216 to 2235 in SEQ ID NO: 5; and
(ii) determining whether said candidate agent modulates expression of a mammalian *FOXC2* gene, such modulation being indicative for an agent capable of regulating mammalian *FOXC2* enhancer activity.

25. An isolated nucleic acid molecule selected from:
(a) nucleic acid molecules comprising a nucleotide sequence as shown in SEQ ID NO: 3;
(b) nucleic acid molecules comprising a nucleotide sequence capable of hybridizing, under stringent hybridization conditions, to a nucleotide sequence complementary the polypeptide coding region of a nucleic acid molecule as defined in (a) and which codes for a variant form of the FOXC2 transcription factor; and
(c) nucleic acid molecules comprising a nucleic acid sequence which is degenerate as a result of the genetic code to a nucleotide sequence as defined in (a) or (b) and which codes for a variant form of the FOXC2 transcription factor.

26. An isolated polypeptide encoded by the nucleic acid according to claim 25.

27. The isolated polypeptide according to claim 26 having an amino acid sequence shown as SEQ ID NO: 4 in the Sequence Listing

28. A vector harboring the nucleic acid molecule according to claim 25.

29. A replicable expression vector which carries and is capable of mediating the expression of a nucleotide sequence according to claim 25.

30. A cultured host cell harboring a vector according to claim 28 or 29.

31. A process for production of a variant form of the FOXC2 transcription factor polypeptide, comprising culturing a host cell according to claim 30 under conditions whereby said polypeptide is produced, and recovering said polypeptide.

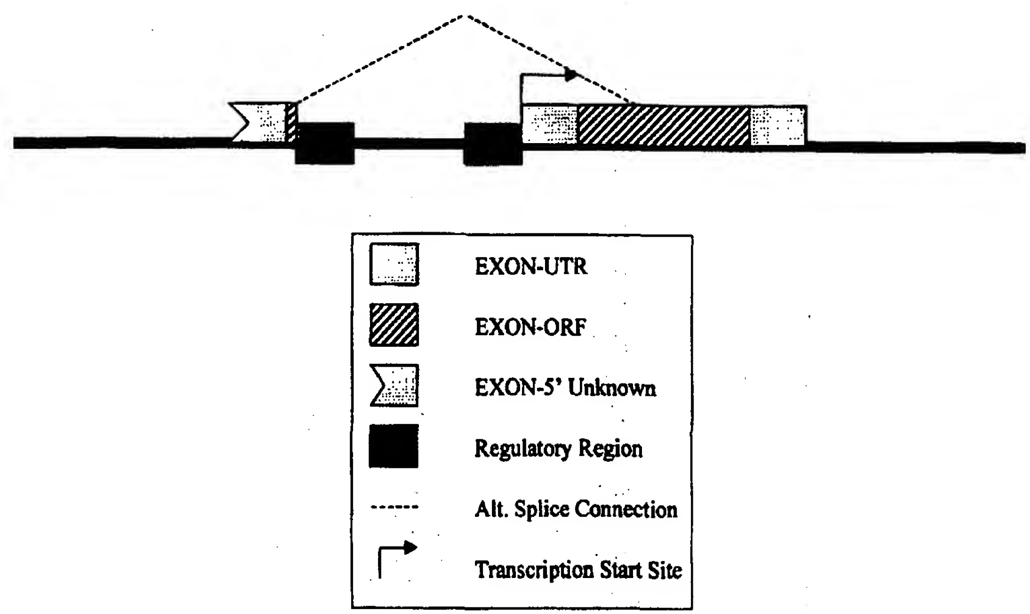
32. A method for identifying an agent capable of regulating expression of the nucleic acid molecule according to claim 25, said method comprising the steps
(i) contacting a candidate agent with the said nucleic acid molecule; and
(ii) determining whether said candidate agent modulates expression of the said nucleic acid molecule.

33. An antisense oligonucleotide having a sequence capable of specifically hybridizing to RNA transcribed by the nucleic acid molecule according to claim 25, so as to prevent translation of the said RNA.

ABSTRACT

The present invention relates an isolated promoter region of the mammalian transcription factor *FOXC2*. The invention also relates to screening methods for agents modulating the expression of *FOXC2* and thereby being potentially useful for the treatment of medical conditions related to obesity. The invention further relates to a previously unknown variant of the human *FOXC2* gene, derived via the use of an alternative promoter, which produces an additional exon that generates a distinct open reading frame via splicing. The alternative gene encodes a variant of the FOXC2 transcription factor, which is lacking a part of the DNA-binding domain and consequently has a potential regulatory function.

Fig. 1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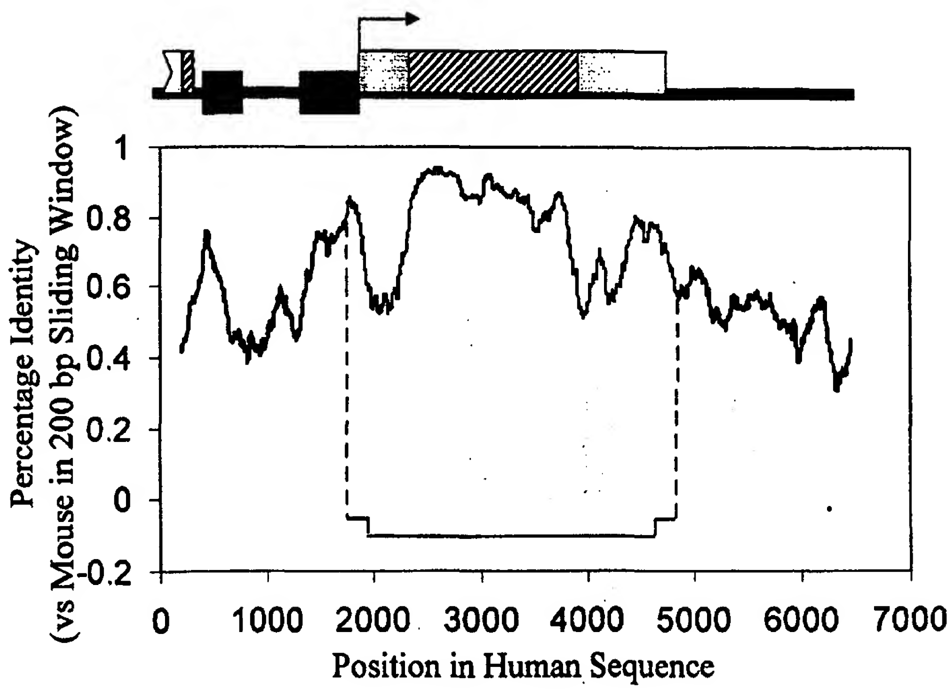
EXON-ORF
EXON-5' Unknown
Regulatory Region
Alt. Splice Connection
Transcription Start Site

Fig. 2



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(vs Mouse in 200 bp Sliding Window)
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0.6
0.4
0.2
0
-0.2
0
1000
2000
3000
4000
5000
6000
7000
Position in Human Sequence

Fig. 3

```
        200                   Splice    E-box-like
HUMAN   AAGGGTGCAAGGAAACCTGAAATACAAATGTTCTCCCTGAAGCCCTCTTCCCTGCCCAAC
MOUSE   CGGAGAAGAAGAAAGACTGAG--ACAAATGTTTTATCTGTCGCCTTCTTCCCTACCCAAC

HUMAN   CAGACCAGCAACTTCCAAAATTCTGCCCGTG---TTTAGCCTTGTTAAAGGGGTGTCTCA
MOUSE   CGGACCAACAACTTCCAGAAGGTTCTGCGAGGCATAGAGCCATTCCGTAGGGACATCTCG

                                                       Forkhead-like
HUMAN   CTCCTTCAGGGAAAGTGGGAAAAG--GGGATCTGATTA----TTGAGGTGTGGAAGGAAT
MOUSE   GTGCTTCTGAGGAAGCGGACCGAGCAGGGATCCGATGACGACTGGAGATGTTGAAGGAAT

                     Forkhead-like                  Ets-like
HUMAN   AAATAATCAGTCCACAAATAAACAAACTGTCC--GGGATTCCTAGAGGGAAGGAGAAATC
MOUSE   AAATA-CCAGTCCACAAATAAACAAACTGTCCCCGGGATTCCTAGAGGGAAGGAGCACGC

                                                   475
HUMAN   CTTGAAG-----GAGATCCAAGTCGCTCCAGGTCTGCCTGCCGAATAATATC
MOUSE   TTGAAGGTCGGGGAACTCCGAGTCGCTGTGCGTCAAGGT-TGGCATAAAATT
```

Fig. 4

```
      (1250)
         |
HUMAN    TGCCATTCCAATC-CAGCGCGTTTGCTTTTGAATCCATTACACCTGGGCCCCCATAATTA
MOUSE    GCCC--TACACGCTCAGTCCGTTTGCTC-TGAACCCATTACAACTAGGCCCCGATAATTA

HUMAN    GGAAATCTAATTATTCGCTTCATCACTCATTAATAA-------GAAAAATGTCCCAGGAT
MOUSE    AGAAATCTAATTATTCGCCTCTTCATCCATTAATAATAATAAAAAAAAAATCTCCAGGCT

HUMAN    CATTGCTACTTACAAGGTCTTTGGGAGAGATATTTTACTCTATTAATCCATTCTATTTTA
MOUSE    CTTTCCTACTTACAAGGTCTTGGGGGCAAATCTCTGCCCAACTTCATCAATTCGATGTTA

HUMAN    TATTTCAAATTGA------TTTTTTTAACAGAGGAAAGTGGCTATC--TTTTTGTTTTG
MOUSE    TATTTCAAACTAAACTTCTTTTTATTTTCCAAAGGAACAGGGTTTTTAATTTTTGCTCTG

HUMAN    GGCATGTGGGCCCATTCACCAAAATGTGATCATAAAATAAATTTTAATAAGATATAACT-
MOUSE    GACACGTGGTCTCGTTAAACAAAATGTGATAATAAAATAAAATTTTATAAGATGTAACTC

HUMAN    -TTTTAAAAAGTTTTCAAGTGAAGACGGAGTCGCCGCGGAGG---------CCGGGGCGG
MOUSE    ATTTTTAAAAGTCCTCAAGTTAACTTGAGCTGGGGGGGGGGGAGATCTGGCTAAGAGCAT

HUMAN    CGGGGTCTTAGAGCCGACGGATTCCTGCGCTCCTCGCCCCGATTGGCGCCGGACTCCTCT
MOUSE    CTGGGTCTTAGAGCCGACGGATTCAGGCGCTCCTCGTTTTGATTGGTGCCATCCTTCTCG
                                                        Forkhead-like
HUMAN    CAGCTGCCGGGTGATTGGCTCAAAGTTCCGGGAGGGGGCGTGGCCCGAGGAAAGTAAAAA
MOUSE    CAGCTGCCAGATGATTGGTGCAAACTTCCTGGAGGGGGCGCGGCCTGAAGAAAGTAAAAA

HUMAN    CTCGCTTTCAGCAAGAAGACTTTTGAAACTTTTCCCAATCCCTAAAAGGGACTTGGCCTC-(1763)
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cagccgatga acagccagga agggtgcaag gaaacctgaa atacaaatgt tctccctgaa 240

gccctcttcc ctgcccaacc agaccagcaa cttccaaaat tctgcccgtg tttagccttg 300

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                1               5                   10

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Leu Gly Val Val Pro Tyr Leu Ser Glu Gln Asn Tyr Tyr Arg Ala Ala
        15                  20                  25

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Gly Ser Tyr Gly Gly Met Ala Ser Pro Met Gly Val Tyr Ser Gly His
    30                  35                  40

ccg gag cag tac agc gcg ggg atg ggc cgc tcc tac gcg ccc tac cac    2414
Pro Glu Gln Tyr Ser Ala Gly Met Gly Arg Ser Tyr Ala Pro Tyr His
45                  50                  55                  60

cac cac cag ccc gcg gcg cct aag gac ctg gtg aag ccg ccc tac agc    2462
His His Gln Pro Ala Ala Pro Lys Asp Leu Val Lys Pro Pro Tyr Ser
                65                  70                  75
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                80                  85                  90

atc acc ttg aac ggc atc tac cag ttc atc atg gac cgc ttc ccc ttc    2558
Ile Thr Leu Asn Gly Ile Tyr Gln Phe Ile Met Asp Arg Phe Pro Phe
        95                  100                 105

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Tyr Arg Glu Asn Lys Gln Gly Trp Gln Asn Ser Ile Arg His Asn Leu
    110                 115                 120

tcg ctc aac gag tgc ttc gtc aag gtg ccc cgc gac gac aag aag ccc    2654
Ser Leu Asn Glu Cys Phe Val Lys Val Pro Arg Asp Asp Lys Lys Pro
125                 130                 135                 140

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Gly Lys Gly Ser Tyr Trp Thr Leu Asp Pro Asp Ser Tyr Asn Met Phe
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Glu Asn Gly Ser Phe Leu Arg Arg Arg Arg Arg Phe Lys Lys Lys Asp
            160                 165                 170

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Val Ser Lys Glu Lys Glu Glu Arg Ala His Leu Lys Glu Pro Pro Pro
        175                 180                 185

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Ala Ala Ser Lys Gly Ala Pro Ala Thr Pro His Leu Ala Asp Ala Pro
    190                 195                 200

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Lys Glu Ala Glu Lys Lys Val Val Ile Lys Ser Glu Ala Ala Ser Pro
205                 210                 215                 220

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                225                 230                 235

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            240                 245                 250

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Asp Gly Ser Leu Pro Glu His His Ala Ala Ala Pro Asn Gly Leu Pro
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Cys Ala Gln Gly Leu Glu Ala Gly Ala Ala Gly Gly Tyr Gln Cys Ser
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Met Arg Ala Met Ser Leu Tyr Thr Gly Ala Glu Arg Pro Ala His Met
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Cys Gln Leu Pro Tyr Arg Ser Thr Pro Pro Leu Tyr Arg His Ala Ala
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Pro Tyr Ser Tyr Asp Cys Thr Lys Tyr
        495                 500

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Ser Ala Gly Met Gly Arg Ser Tyr Ala Pro Tyr His His His Gln Pro
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Gly Ile Tyr Gln Phe Ile Met Asp Arg Phe Pro Phe Tyr Arg Glu Asn
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Lys Gln Gly Trp Gln Asn Ser Ile Arg His Asn Leu Ser Leu Asn Glu
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Cys Phe Val Lys Val Pro Arg Asp Asp Lys Lys Pro Gly Lys Gly Ser
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Tyr Trp Thr Leu Asp Pro Asp Ser Tyr Asn Met Phe Glu Asn Gly Ser
145 150 155 160
Phe Leu Arg Arg Arg Arg Arg Phe Lys Lys Lys Asp Val Ser Lys Glu
165 170 175
Lys Glu Glu Arg Ala His Leu Lys Glu Pro Pro Pro Ala Ala Ser Lys
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Gly Ala Pro Ala Thr Pro His Leu Ala Asp Ala Pro Lys Glu Ala Glu
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Ile Thr Lys Val Glu Thr Leu Ser Pro Glu Ser Ala Leu Gln Gly Ser
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Pro Glu His His Ala Ala Ala Pro Asn Gly Leu Pro Gly Phe Ser Val
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Glu Asn Ile Met Thr Leu Arg Thr Ser Pro Pro Gly Gly Glu Leu Ser
275 280 285
Pro Gly Ala Gly Arg Ala Gly Leu Val Val Pro Pro Leu Ala Leu Pro
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Tyr Ala Ala Ala Pro Pro Ala Ala Tyr Gly Gln Pro Cys Ala Gln Gly
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Ser Leu Tyr Thr Gly Ala Glu Arg Pro Ala His Met Cys Val Pro Pro
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Leu Ser Ala Leu Asn Leu Ala Ala Gly Gln Glu Gly Ala Leu Ala Ala
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Thr Gly His His His Gln His His Gly His His His Pro Gln Ala Pro
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Tyr Gln Phe Ile Met Asp Arg Phe Pro Phe Tyr Arg Glu Asn Lys Gln
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ggc tgg cag aac agc atc cgc cac aac ctc tcg ctc aac gag tgc ttc    324
Gly Trp Gln Asn Ser Ile Arg His Asn Leu Ser Leu Asn Glu Cys Phe
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gtc aag gtg ccc cgc gac gac aag aag ccc ggc aag ggc agt tac tgg    372
Val Lys Val Pro Arg Asp Asp Lys Lys Pro Gly Lys Gly Ser Tyr Trp
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acc ctg gac ccg gac tcc tac aac atg ttc gag aac ggc agc ttc ctg    420
Thr Leu Asp Pro Asp Ser Tyr Asn Met Phe Glu Asn Gly Ser Phe Leu
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cgg cgc cgg cgg cgc ttc aaa aag aag gac gtg tcc aag gag aag gag    468
Arg Arg Arg Arg Arg Phe Lys Lys Lys Asp Val Ser Lys Glu Lys Glu
     80                  85                  90

gag cgg gcc cac ctc aag gag ccg ccc ccg gcg gcg tcc aag ggc gcc    516
Glu Arg Ala His Leu Lys Glu Pro Pro Pro Ala Ala Ser Lys Gly Ala
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ccg gcc acc ccc cac cta gcg gac gcc ccc aag gag gcc gag aag aag    564
Pro Ala Thr Pro His Leu Ala Asp Ala Pro Lys Glu Ala Glu Lys Lys
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Lys Val Glu Thr Leu Ser Pro Glu Ser Ala Leu Gln Gly Ser Pro Arg
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Ser Ala Ala Ser Thr Pro Ala Gly Ser Pro Asp Gly Ser Leu Pro Glu
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cac cac gcc gcg gcg ccc aac ggg ctg cct ggc ttc agc gtg gag aac    756
His His Ala Ala Ala Pro Asn Gly Leu Pro Gly Phe Ser Val Glu Asn
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atc atg acc ctg cga acg tcg ccg ccg ggc gga gag ctg agc ccg ggg    804
Ile Met Thr Leu Arg Thr Ser Pro Pro Gly Gly Glu Leu Ser Pro Gly
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gcc gga cgc gcg ggc ctg gtg gtg ccg ccg ctg gcg ctg cca tac gcc    852
Ala Gly Arg Ala Gly Leu Val Val Pro Pro Leu Ala Leu Pro Tyr Ala
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gcc gcg ccg ccc gcc gcc tac ggc cag ccg tgc gct cag ggc ctg gag    900
Ala Ala Pro Pro Ala Ala Tyr Gly Gln Pro Cys Ala Gln Gly Leu Glu
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gcc ggg gcc gcc ggg ggc tac cag tgc agc atg cga gcg atg agc ctg    948
Ala Gly Ala Ala Gly Gly Tyr Gln Cys Ser Met Arg Ala Met Ser Leu
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Tyr Thr Gly Ala Glu Arg Pro Ala His Met Cys Val Pro Pro Ala Leu
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gac gag gcc ctc tcg gac cac ccg agc ggc ccc acg tcg ccc ctg agc 1044
Asp Glu Ala Leu Ser Asp His Pro Ser Gly Pro Thr Ser Pro Leu Ser
275 280 285

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Ala Leu Asn Leu Ala Ala Gly Gln Glu Gly Ala Leu Ala Ala Thr Gly
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cac cac cac cag cac cac ggc cac cac cac ccg cag gcg ccg ccg ccc 1140
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Pro Pro Ala Pro Gln Pro Gln Pro Thr Pro Gln Pro Gly Ala Ala Ala
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Leu Pro Gly His Thr Phe Ala Ala Gln Gln Gln Thr Phe Pro Asn Val
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Gly Glu Ser Gln Val Ser Gly Asn Ala Ser Cys Gln Leu Pro Tyr Arg
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Ser Thr Pro Pro Leu Tyr Arg His Ala Ala Pro Tyr Ser Tyr Asp Cys
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Thr Lys Tyr
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Gln Asn Ser Ile Arg His Asn Leu Ser Leu Asn Glu Cys Phe Val Lys
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Val Pro Arg Asp Asp Lys Lys Pro Gly Lys Gly Ser Tyr Trp Thr Leu
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Asp Pro Asp Ser Tyr Asn Met Phe Glu Asn Gly Ser Phe Leu Arg Arg
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Arg Arg Arg Phe Lys Lys Lys Asp Val Ser Lys Glu Lys Glu Glu Arg
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Thr Pro His Leu Ala Asp Ala Pro Lys Glu Ala Glu Lys Lys Val Val
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Ile Lys Ser Glu Ala Ala Ser Pro Ala Leu Pro Val Ile Thr Lys Val
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Glu Thr Leu Ser Pro Glu Ser Ala Leu Gln Gly Ser Pro Arg Ser Ala
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Ala Ala Ala Pro Asn Gly Leu Pro Gly Phe Ser Val Glu Asn Ile Met
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Ala Ala Gly Gly Tyr Gln Cys Ser Met Arg Ala Met Ser Leu Tyr Thr
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Gly Ala Glu Arg Pro Ala His Met Cys Val Pro Pro Ala Leu Asp Glu
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Ala Leu Ser Asp His Pro Ser Gly Pro Thr Ser Pro Leu Ser Ala Leu
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Asn Leu Ala Ala Gly Gln Glu Gly Ala Leu Ala Ala Thr Gly His His
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His Gln His His Gly His His His Pro Gln Ala Pro Pro Pro Pro Pro
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Ala Ala Ser Trp Tyr Leu Asn His Ser Gly Asp Leu Asn His Leu Pro
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Gly His Thr Phe Ala Ala Gln Gln Gln Thr Phe Pro Asn Val Arg Glu
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Met Phe Asn Ser His Arg Leu Gly Ile Glu Asn Ser Thr Leu Gly Glu
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Ser Gln Val Ser Gly Asn Ala Ser Cys Gln Leu Pro Tyr Arg Ser Thr
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atc tac cag ttc atc atg gac cgt ttc ccc ttc tac cgc gag aac aag   757
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Phe Val Lys Val Pro Arg Asp Asp Lys Lys Pro Gly Lys Gly Ser Tyr
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Ser Trp Tyr Leu Asn His Gly Gly Asp Leu Ser His Leu Pro Gly His
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 65                  70                  75                  80

atc acc atg gcc atc cag aac gcg ccc gag aag aag atc acc ttg aac    288
Ile Thr Met Ala Ile Gln Asn Ala Pro Glu Lys Lys Ile Thr Leu Asn
                 85                  90                  95

ggc atc tac cag ttc atc atg gac cgc ttc ccc ttc tac cgg gag aac    336
Gly Ile Tyr Gln Phe Ile Met Asp Arg Phe Pro Phe Tyr Arg Glu Asn
            100                 105                 110

aag cag ggc tgg cag aac agc atc cgc cac aac ctc tcg ctc aac gag    384
Lys Gln Gly Trp Gln Asn Ser Ile Arg His Asn Leu Ser Leu Asn Glu
        115                 120                 125

tgc ttc gtc aag gtg ccc cgc gac gac aag aag ccc ggc aag ggc agt    432
Cys Phe Val Lys Val Pro Arg Asp Asp Lys Lys Pro Gly Lys Gly Ser
    130                 135                 140

tac tgg acc ctg gac ccg gac tcc tac aac atg ttc gag aac ggc agc    480
Tyr Trp Thr Leu Asp Pro Asp Ser Tyr Asn Met Phe Glu Asn Gly Ser
145                 150                 155                 160

ttc ctg cgg cgc cgg cgg cgc ttc aaa aag aag gac gtg tcc aag gag    528
Phe Leu Arg Arg Arg Arg Arg Phe Lys Lys Lys Asp Val Ser Lys Glu
                165                 170                 175

aag gag gag cgg gcc cac ctc aag gag ccg ccc ccg gcg gcg tcc aag    576
Lys Glu Glu Arg Ala His Leu Lys Glu Pro Pro Pro Ala Ala Ser Lys
            180                 185                 190

ggc gcc ccg gcc acc ccc cac cta gcg gac gcc ccc aag gag gcc gag    624
Gly Ala Pro Ala Thr Pro His Leu Ala Asp Ala Pro Lys Glu Ala Glu
        195                 200                 205

aag aag gtg gtg atc aag agc gag gcg gcg tcc ccg gcg ctg ccg gtc    672
Lys Lys Val Val Ile Lys Ser Glu Ala Ala Ser Pro Ala Leu Pro Val
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atc acc aag gtg gag acg ctg agc ccc gag agc gcg ctg cag ggc agc    720
Ile Thr Lys Val Glu Thr Leu Ser Pro Glu Ser Ala Leu Gln Gly Ser
225                 230                 235                 240

ccg cgc agc gcg gcc tcc acg ccc gcc ggc tcc ccc gac ggt tcg ctg    768
Pro Arg Ser Ala Ala Ser Thr Pro Ala Gly Ser Pro Asp Gly Ser Leu
                245                 250                 255

ccg gag cac cac gcc gcg gcg ccc aac ggg ctg cct ggc ttc agc gtg    816
Pro Glu His His Ala Ala Ala Pro Asn Gly Leu Pro Gly Phe Ser Val
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gag aac atc atg acc ctg cga acg tcg ccg ccg ggc gga gag ctg agc    864
Glu Asn Ile Met Thr Leu Arg Thr Ser Pro Pro Gly Gly Glu Leu Ser
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ccg ggg gcc gga cgc gcg ggc ctg gtg gtg ccg ccg ctg gcg ctg cca    912
Pro Gly Ala Gly Arg Ala Gly Leu Val Val Pro Pro Leu Ala Leu Pro
    290                 295                 300

tac gcc gcc gcg ccg ccc gcc gcc tac ggc cag ccg tgc gct cag ggc    960
Tyr Ala Ala Ala Pro Pro Ala Ala Tyr Gly Gln Pro Cys Ala Gln Gly
305                 310                 315                 320

ctg gag gcc ggg gcc gcc ggg ggc tac cag tgc agc atg cga gcg atg    1008
Leu Glu Ala Gly Ala Ala Gly Gly Tyr Gln Cys Ser Met Arg Ala Met
                325                 330                 335

agc ctg tac acc ggg gcc gag cgg ccg gcg cac atg tgc gtc ccg ccc    1056
Ser Leu Tyr Thr Gly Ala Glu Arg Pro Ala His Met Cys Val Pro Pro
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gcc ctg gac gag gcc ctc tcg gac cac ccg agc ggc ccc acg tcg ccc    1104
Ala Leu Asp Glu Ala Leu Ser Asp His Pro Ser Gly Pro Thr Ser Pro
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ctg agc gct ctc aac ctc gcc gcc ggc cag gag ggc gcg ctc gcc gcc    1152
Leu Ser Ala Leu Asn Leu Ala Ala Gly Gln Glu Gly Ala Leu Ala Ala
    370                 375                 380

acg ggc cac cac cac cag cac cac ggc cac cac cac ccg cag gcg ccg    1200
Thr Gly His His His Gln His His Gly His His His Pro Gln Ala Pro
385                 390                 395                 400

ccg ccc ccg ccg gct ccc cag ccc cag ccg acg ccg cag ccc ggg gcc    1248
Pro Pro Pro Pro Ala Pro Gln Pro Gln Pro Thr Pro Gln Pro Gly Ala
                405                 410                 415

gcc gcg gcg cag gcg gcc tcc tgg tat ctc aac cac agc ggg gac ctg    1296
Ala Ala Ala Gln Ala Ala Ser Trp Tyr Leu Asn His Ser Gly Asp Leu
            420                 425                 430

aac cac ctc ccc ggc cac acg ttc gcg gcc cag cag caa act ttc ccc    1344
Asn His Leu Pro Gly His Thr Phe Ala Ala Gln Gln Gln Thr Phe Pro
        435                 440                 445

aac gtg cgg gag atg ttc aac tcc cac cgg ctg ggg att gag aac tcg    1392
Asn Val Arg Glu Met Phe Asn Ser His Arg Leu Gly Ile Glu Asn Ser
    450                 455                 460

acc ctc ggg gag tcc cag gtg agt ggc aat gcc agc tgc cag ctg ccc    1440
Thr Leu Gly Glu Ser Gln Val Ser Gly Asn Ala Ser Cys Gln Leu Pro
465                 470                 475                 480

tac aga tcc acg ccg cct ctc tat cgc cac gca gcc ccc tac tcc tac    1488
Tyr Arg Ser Thr Pro Pro Leu Tyr Arg His Ala Ala Pro Tyr Ser Tyr
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        35                  40                  45
Ser Ala Gly Met Gly Arg Ser Tyr Ala Pro Tyr His His His Gln Pro
    50                  55                  60
Ala Ala Pro Lys Asp Leu Val Lys Pro Pro Tyr Ser Tyr Ile Ala Leu
65                  70                  75                  80
Ile Thr Met Ala Ile Gln Asn Ala Pro Glu Lys Lys Ile Thr Leu Asn
                85                  90                  95
Gly Ile Tyr Gln Phe Ile Met Asp Arg Phe Pro Phe Tyr Arg Glu Asn
            100                 105                 110
Lys Gln Gly Trp Gln Asn Ser Ile Arg His Asn Leu Ser Leu Asn Glu
        115                 120                 125
Cys Phe Val Lys Val Pro Arg Asp Asp Lys Lys Pro Gly Lys Gly Ser
    130                 135                 140
Tyr Trp Thr Leu Asp Pro Asp Ser Tyr Asn Met Phe Glu Asn Gly Ser
145                 150                 155                 160
Phe Leu Arg Arg Arg Arg Arg Phe Lys Lys Lys Asp Val Ser Lys Glu
                165                 170                 175
Lys Glu Glu Arg Ala His Leu Lys Glu Pro Pro Pro Ala Ala Ser Lys
            180                 185                 190
Gly Ala Pro Ala Thr Pro His Leu Ala Asp Ala Pro Lys Glu Ala Glu
        195                 200                 205
Lys Lys Val Val Ile Lys Ser Glu Ala Ala Ser Pro Ala Leu Pro Val
    210                 215                 220
Ile Thr Lys Val Glu Thr Leu Ser Pro Glu Ser Ala Leu Gln Gly Ser
225                 230                 235                 240
Pro Arg Ser Ala Ala Ser Thr Pro Ala Gly Ser Pro Asp Gly Ser Leu
                245                 250                 255
Pro Glu His His Ala Ala Ala Pro Asn Gly Leu Pro Gly Phe Ser Val
            260                 265                 270
Glu Asn Ile Met Thr Leu Arg Thr Ser Pro Pro Gly Gly Glu Leu Ser
        275                 280                 285
Pro Gly Ala Gly Arg Ala Gly Leu Val Val Pro Pro Leu Ala Leu Pro
    290                 295                 300
Tyr Ala Ala Ala Pro Pro Ala Ala Tyr Gly Gln Pro Cys Ala Gln Gly
305                 310                 315                 320
Leu Glu Ala Gly Ala Ala Gly Gly Tyr Gln Cys Ser Met Arg Ala Met
                325                 330                 335
Ser Leu Tyr Thr Gly Ala Glu Arg Pro Ala His Met Cys Val Pro Pro
            340                 345                 350
Ala Leu Asp Glu Ala Leu Ser Asp His Pro Ser Gly Pro Thr Ser Pro
        355                 360                 365
Leu Ser Ala Leu Asn Leu Ala Ala Gly Gln Glu Gly Ala Leu Ala Ala
    370                 375                 380
Thr Gly His His His Gln His His Gly His His His Pro Gln Ala Pro
385                 390                 395                 400
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Pro Pro Pro Pro Ala Pro Gln Pro Gln Pro Thr Pro Gln Pro Gly Ala
                405                 410                 415
Ala Ala Ala Gln Ala Ala Ser Trp Tyr Leu Asn His Ser Gly Asp Leu
            420                 425                 430
Asn His Leu Pro Gly His Thr Phe Ala Ala Gln Gln Gln Thr Phe Pro
        435                 440                 445
Asn Val Arg Glu Met Phe Asn Ser His Arg Leu Gly Ile Glu Asn Ser
    450                 455                 460
Thr Leu Gly Glu Ser Gln Val Ser Gly Asn Ala Ser Cys Gln Leu Pro
465                 470                 475                 480
Tyr Arg Ser Thr Pro Pro Leu Tyr Arg His Ala Ala Pro Tyr Ser Tyr
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Asp Cys Thr Lys Tyr
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